

The Duration of Pretreatment With Ticlopidine Prior to Stenting Is Associated With the Risk of Procedure-Related Non-Q-Wave Myocardial Infarctions

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Objectives. This study sought to determine whether the duration of pretreatment with the adenosine diphosphate receptor antagonist ticlopidine prior to intracoronary stenting is associated with the incidence of procedure-related non-Q-wave myocardial infarctions (MIs).

Background. Dual antiplatelet therapy with ticlopidine and aspirin is routinely used with stenting, although ticlopidine is commonly not begun until the day of the procedure. Periprocedural MIs are at least partially platelet-dependent events. As the maximal platelet inhibitory effects of this drug take 2 to 3 days to be realized, we hypothesized that longer treatment prior to stenting would be associated with lower rates of procedure-related MIs.

Methods. We reviewed outcomes in 175 consecutive patients treated with ticlopidine prior to stenting at the Cleveland Clinic Foundation. Those patients with an elevation in creatine kinase above our laboratory normal (>210 IU/L) with $\geq 4\%$ MB fraction on routine evaluation were defined as having a non-Q-wave MI.

Results. There were 28 patients (16%) who had a non-Q-wave MI. Longer duration of ticlopidine pretreatment was strongly associated with a lower incidence of procedure-related non-Q-wave MIs (duration of pretreatment <1 day, 29% had MI; 1 to 2 days, 14%; ≥ 3 days, 5%; chi-square for trend = 9.6; $p = 0.002$). Ticlopidine pretreatment of ≥ 3 days was associated with a significant reduction in the risk of non-Q-wave MI (unadjusted odds ratio 0.18, 95% confidence interval = 0.04 to 0.78, $p = 0.01$) compared with pretreatment of <3 days.

Conclusions. Among patients undergoing intracoronary stenting, beginning ticlopidine therapy several days prior to the procedure is associated with a reduced risk of procedural non-Q-wave MIs.

(J Am Coll Cardiol 1998;32:1366–70)
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Non-Q-wave myocardial infarctions (MIs) can occur in up to one-third of patients after percutaneous coronary revascularization procedures (1). Although the clinical significance of these events is controversial, recent studies involving $>10,000$ patients in aggregate have suggested that even seemingly minor elevations in myocardial enzymes after percutaneous transluminal coronary angioplasty (PTCA) are associated with increased late mortality, a higher risk of subsequent cardiac events, and higher costs (2–4). The mechanism behind the myonecrosis associated with percutaneous revascularization procedures is at least in part distal embolization. Observational reports of high rates of periprocedural infarcts in thrombus-

laden lesions support platelet-rich thromboemboli as a major source of the embolic debris (5), and animal studies have confirmed that intracoronary platelet microaggregates can lead to MI (6). However, some of the most compelling evidence supporting platelet thromboemboli as a major contributor to procedure-related infarcts comes from angioplasty trials utilizing aggressive platelet inhibition with glycoprotein (GP) IIb/IIIa receptor antagonists (7–11). In these trials patients treated with GPIIb/IIIa inhibitors experienced up to a 50% decrease in periprocedural MIs compared with those receiving standard aspirin and heparin therapy.

Patients undergoing coronary stent implantation may be at increased risk of a non-Q-wave MI than those treated with balloon angioplasty alone due to increased platelet activation caused by the intracoronary metallic stent (12,13). This contention is supported by a recent report of a greater than 20% incidence of non-Q-wave MI in stent-treated patients—nearly 70% greater than that observed in those treated with balloon angioplasty alone (14,15).

Almost all stent-treated patients today receive combination

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Manuscript received April 17, 1998; revised manuscript received June 19, 1998, accepted July 6, 1998.

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Abbreviations and Acronyms

ADP	=	adenosine diphosphate
GPIIb/IIIa	=	glycoprotein IIb/IIIa
PTCA	=	percutaneous transluminal coronary angioplasty

antiplatelet therapy with ticlopidine and aspirin because of its established benefit in the prevention of stent thrombosis (16). This combination provides a synergistic inhibition of platelet aggregation (17,18), although it does not achieve its full inhibitory potential until after 3 to 5 days of therapy due to the delayed onset of ticlopidine's antiplatelet effects (19). Since subacute stent thrombosis typically occurs at 5 to 6 days after stent implantation (20), beginning ticlopidine at the time of the procedure provides adequate protection from this complication. However, this dosing regimen is unable to provide additional antiplatelet protection at the time of the procedure, and therefore is unable to potentially further decrease the risk of periprocedural complications including non-Q-wave MIs.

We postulated that patients receiving chronic aspirin therapy who were also pretreated with ticlopidine for several days prior to stenting would experience a decreased incidence of procedural non-Q-wave MIs due to the time-dependent development of enhanced platelet inhibition at the time of stent implantation. To test this hypothesis we performed an analysis of consecutive patients at our institution who received an intracoronary stent and ticlopidine pretreatment of variable duration before the procedure.

Methods

Patient sample. All data analyzed in this study were obtained prospectively; demographic, procedural and outcome information about all patients undergoing percutaneous coronary revascularization procedures at the Cleveland Clinic Foundation are prospectively entered into an electronic database. All patients provide informed consent before the procedure. From this database, 1,207 consecutive patients were identified who had an intracoronary stent placed between August 1995 and December 1996. From this cohort, 103 patients who underwent a concomitant atherectomy were eliminated due to their recognized association with an increased incidence of non-Q-wave MIs. Another 38 patients with an MI within the preceding 24 h were also excluded. Eighty-four patients were excluded for receiving a stent as a bailout indication, and another 207 patients were excluded for abciximab treatment. From the remaining 775 patients, 175 received preprocedural ticlopidine. Confirmation of pretreatment and determination of the duration of pretreatment was through medical record review. These 175 patients were divided a priori into three groups based on the duration of ticlopidine pretreatment: ≥ 3 days before the procedure, 1 to 2 days, or < 1 day if started prior to but on the same day as stent placement.

Table 1. Baseline Patient, Procedural and Lesion Characteristics According to Duration of Ticlopidine Pretreatment

	Duration of Ticlopidine Pretreatment		
	0 Days	1–2 Days	≥ 3 Days
No. of patients	52	78	45
Mean age (yr)	62	61	59.5
Mean LVEF (%)	53.1	53.8	53.8
Unstable angina (%)	57.7	76.9	68.9
Recent MI (%)	19.2	15.4	6.7
Diabetes (%)	15.4	25.6	31.0
Current smoker (%)	17.3	17.9	26.6
Previous bypass (%)	28.8	33.3	31.1
Average no. of treated vessels	1.7	1.6	1.5
Vein graft target vessel (%)	25.0	26.9	20.0
Restenotic lesion (%)	13.5	2.6	15.5
B2 or C lesion (%)	61.0	44.9	40.0
Side branch closure (%)	0	0	0
Transient vessel closure (%)	3.8	0	0

Recent MI = within 1–7 days. LVEF = left ventricular ejection fraction.

Ascertainment of procedure-related MI. Creatine kinase (CK) levels are routinely and systematically measured at our institution among all patients undergoing coronary intervention at 8 h and the morning (12 to 25 h) postprocedure. Creatine kinase MB isoenzyme levels are determined in all patients with CK levels above 100 IU/L. For the purposes of this study, any elevation in CK levels above our laboratory's normal range (210 IU/L) with an MB fraction of $\geq 4\%$ was considered diagnostic for a non-Q-wave MI.

Statistical methods. The association between duration of ticlopidine pretreatment and occurrence of procedural non-Q-wave MI was tested using the Mantel-Haenszel extension test for trend (21). Because patients who received shorter durations of ticlopidine pretreatment were more likely to have B2 or C lesions, to undergo stenting of saphenous vein grafts and to have had a recent MI, stratified analyses were performed, again using the extension test. Logistic regression analyses (22) were also used to adjust for potential confounders. No more than two covariates were considered in each model in order to avoid overfitting. Considered significant were p values of < 0.05 . All analyses were performed using the SAS 6.12 system (SAS Inc.).

Results

Of the 175 patients studied, 52 patients first received ticlopidine on the same day as the procedure, 78 patients 1 or 2 days before and 45 patients for 3 or more days. Patients receiving ticlopidine pretreatment were distributed among all interventional cardiologists at our institution. The baseline characteristics of the patients comprising each group are noted in Table 1. Patients receiving ≥ 3 days of ticlopidine were more frequently diabetic, smokers and had unstable angina, but they also had shorter average lesion lengths, fewer recent MIs (within 1 to 7 days), fewer saphenous vein graft lesions and less frequent modified American College of Cardiology/American

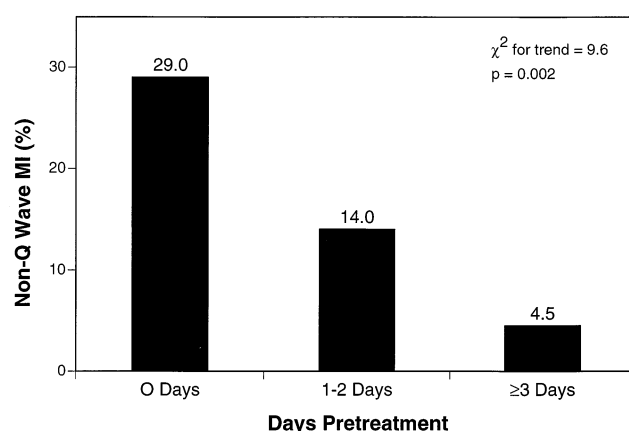


Figure 1. Incidence of procedure-related non-Q-wave MI in patient groups based on the duration of ticlopidine pretreatment. Chi-squared for trend, $p = 0.002$.

Heart Association (ACC/AHA) criteria B2 or C lesions compared with those beginning treatment on the day of the procedure.

There were no major in-laboratory ischemic complications (death, Q-wave MI, emergency bypass surgery) within the study population. There were 28 procedure-related non-Q-wave MIs as defined by an abnormal elevation in CKs with an associated positive MB fraction. Fifteen events occurred in those patients first receiving ticlopidine on the day of the procedure (29%), 11 events in patients beginning ticlopidine 1 to 2 days before the procedure (14%) and only 2 events in those pretreated for 3 or more days (5%) (chi-square for trend = 9.6, $p = 0.002$) (Fig. 1). The incidence of non-Q-wave MIs of various sizes among the patient groups is shown in Table 2. Among subgroups of patients with or without recent MI, saphenous vein stenting and B2 or C lesions, a similar trend of increasing protection with a longer duration of ticlopidine pretreatment was seen (Table 3).

Comparing the 45 patients who received ≥3 days of pretreatment with the 130 pretreated for <3 days, the unadjusted odds ratio for the risk of non-Q-wave MI was 0.18 (95% confidence interval [CI] = 0.04 to 0.78, $p = 0.01$). After adjusting for saphenous vein graft (SVG) and modified ACC/AHA class, the adjusted odds ratio was 0.19 (95% CI = 0.04 to 0.83, $p = 0.03$). In a separate model adjusting for recent MI,

Table 2. Frequency of Small and Large Non-Q-Wave MIs in Each Patient Group

Days Pretreatment	Percent of Patients With Different Sizes of Non-Q-Wave MIs			
	1-2 × Normal CK	2-3 × Normal CK	3-5 × Normal CK	>5 × Normal CK
0 days	19	2	2	6
1-2 days	11.4	1.3	0	1.3
≥3 days	2.2	2.2	0	0

CK = creatinine kinase; MI = myocardial infarction.

Table 3. Frequency of Procedure-Related Non-Q-Wave MI According to Duration of Pretreatment With Ticlopidine: Results of Stratified Analyses

Patients	Percent With Non-Q MI			Chi-square for Trend	p
	0 Days	1-2 Days	≥3 Days		
With SVG	46	23	0	5.5	0.02
Without SVG	23	10	6	4.3	0.04
With recent MI	20	17	0	0.6	0.43
Without recent MI	31	14	5	9.2	0.002
With B2 or C lesions	28	14	11	2.1	0.15
With A or B1 lesions	30	14	0	8.3	0.004

Recent MI = within 1-7 days. MI = myocardial infarction; SVG = saphenous vein graft.

the adjusted odds ratio was 0.17 (95% CI = 0.04 to 0.77, $p = 0.02$).

In secondary analyses the population was divided into the 123 patients who received ≥1 day of ticlopidine pretreatment and the 52 patients beginning ticlopidine on the day of the procedure. The unadjusted odds ratio for the risk of a non-Q-wave MI in the pretreated group was 0.32 (95% CI = 0.14 to 0.72, $p = 0.005$). After adjusting for SVG and modified ACC/AHA class, the adjusted odds ratio was 0.31 (95% CI = 0.13 to 0.72, $p = 0.006$).

There were two major bleeding complications among the study population. Both patients required a transfusion of 2 U of packed red blood cells. One patient received ticlopidine pretreatment for ≥3 days and the other was pretreated for 1 to 2 days before the procedure.

Discussion

This analysis of stent-treated patients is the first to suggest that ticlopidine pretreatment of adequate duration to allow for the development of near maximal platelet inhibition is associated with a markedly decreased incidence of procedure-related non-Q-wave MI. The results are consistent with a “dose/duration-effect,” that is, as the duration of pretreatment increased from 1 to 3 or more days, with the associated development of increasing antiplatelet protection by ticlopidine, there was a time-dependent reduction in non-Q-wave MIs.

Mechanism. Thienopyridine compounds such as ticlopidine and its more recently developed analog, clopidogrel, selectively inhibit the platelet adenosine diphosphate (ADP) receptor. They are inactive in vitro, and full antiplatelet action of ticlopidine in vivo requires 3 to 5 days of oral administration (19,23). Ticlopidine inhibits both ADP-induced alpha-granule secretion and ADP-induced binding of fibrinogen to the GPIIb/IIIa complex without directly interfering with the GPIIb/IIIa receptor site (24). Although the thienopyridines do not completely prevent fibrinogen binding and platelet aggregation as do the direct GPIIb/IIIa inhibitors, recent studies suggest that they inhibit binding to an extent that impairs the formation of the platelet-to-platelet contacts necessary for

normal thrombus growth and stabilization (25). Animal studies evaluating the combination of ticlopidine and aspirin have demonstrated a synergistic antithrombotic effect (18,26), and a similar interaction has been confirmed in humans (17,27).

The time-dependent development of improved antithrombotic effects in patients pretreated with ticlopidine and aspirin have been confirmed in several clinical studies (17,28,29). Rupprecht et al. (17) demonstrated that only patients treated with both ticlopidine and aspirin, compared with either agent alone, experienced a significant reduction in collagen-induced platelet aggregation by 7 days of therapy. In another study by Gregorini et al. (28), both thrombin generation and platelet activation were significantly reduced before and after PTCA in patients receiving ≥ 72 h of ticlopidine pretreatment, but not in those pretreated for ≤ 24 h. As previous studies have demonstrated a significant association between markers of platelet activation before PTCA and acute ischemic complications, these results support a basis for our findings and suggest a greater clinical role for combined antiplatelet therapy before all percutaneous coronary revascularization procedures (30).

The beneficial role of platelet inhibition in PTCA has been consistently demonstrated in a number of studies of GPIIb/IIIa inhibitors (7–11). Cost, however, remains a major limitation to the widespread use of adjunctive GPIIb/IIIa inhibition therapy during percutaneous interventions. Combination antiplatelet therapy with ticlopidine or clopidogrel may prove to be an effective, low cost alternative in specific subgroups of patients able to begin therapy prior to the procedure.

Study limitations. Although all data were obtained prospectively, this was an observational study and therefore suffers from all the potential limitations of such a study. Despite attempting to control for baseline differences between patient groups, there are potentially other, unmeasured differences in baseline risk factors that may have confounded the association between duration of ticlopidine pretreatment and the incidence of periprocedural MI.

For this study, the definition of a procedural non-Q-wave MI was defined as any abnormal increase in CK with a positive MB fraction. Although elevations of this level are associated with an increased risk of an adverse long-term outcome (31), a recent consensus statement defined a procedure-related MI as an elevation of three times the laboratory normal (3).

The study sample is quite small with data collected over 1 year ago. At the time these patients were being treated, preprocedural ticlopidine was not routinely used at our institution.

Conclusions. The association we observed between duration of ticlopidine pretreatment and risk of procedure-related MI meets those of a valid clinical epidemiologic relationship. The association was strong, with a nearly 80% reduction in risk noted as the duration of therapy increased. A temporal dose-response relationship was demonstrated. The association persisted even after adjusting for potential confounders. Because all data were obtained routinely, uniformly and prospectively among all potentially eligible patients, we doubt a major selection or ascertainment bias exists. The relationship is biologically plausible and is consistent with previous work.

Ticlopidine and aspirin provide synergistic platelet inhibitory effects. When combination therapy is begun early enough before coronary stenting to allow for the development of ticlopidine's maximal platelet inhibitory effects, there appears to be an associated marked decrease in the incidence of procedural non-Q-wave MIs. Randomized, prospective studies are now needed to define the optimal dosing regimens and the degree of clinical benefit achieved by pretreatment with this kind of dual antiplatelet therapy.

Drs. Steinhubl, Lauer, and Topol designed the study. Drs. Steinhubl and Mukherjee carried out all data acquisition. Drs. Steinhubl, Lauer and Ellis performed the data analysis. Drs. Steinhubl and Lauer took primary responsibility for writing the manuscript. Drs. Mukherjee, Moliterno, Lincoff, Ellis and Topol extensively reviewed and modified the manuscript.

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